

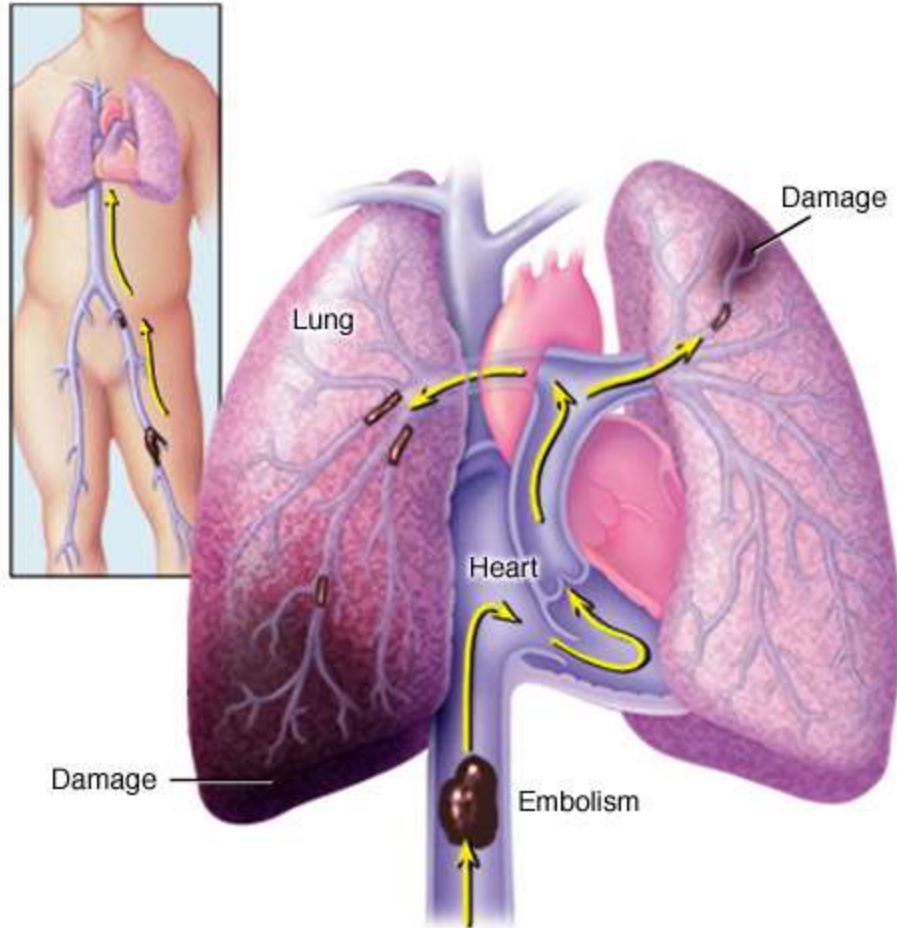
Supportive module 3 "Basics of diagnosis, treatment and prevention  
of major pulmonary diseases "

# Pulmonary Embolism

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

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# Plan of the Lecture



- Definition
- Epidemiology
- Risk Factors and Etiology
- Mechanisms
- Classification
- Clinical presentation
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

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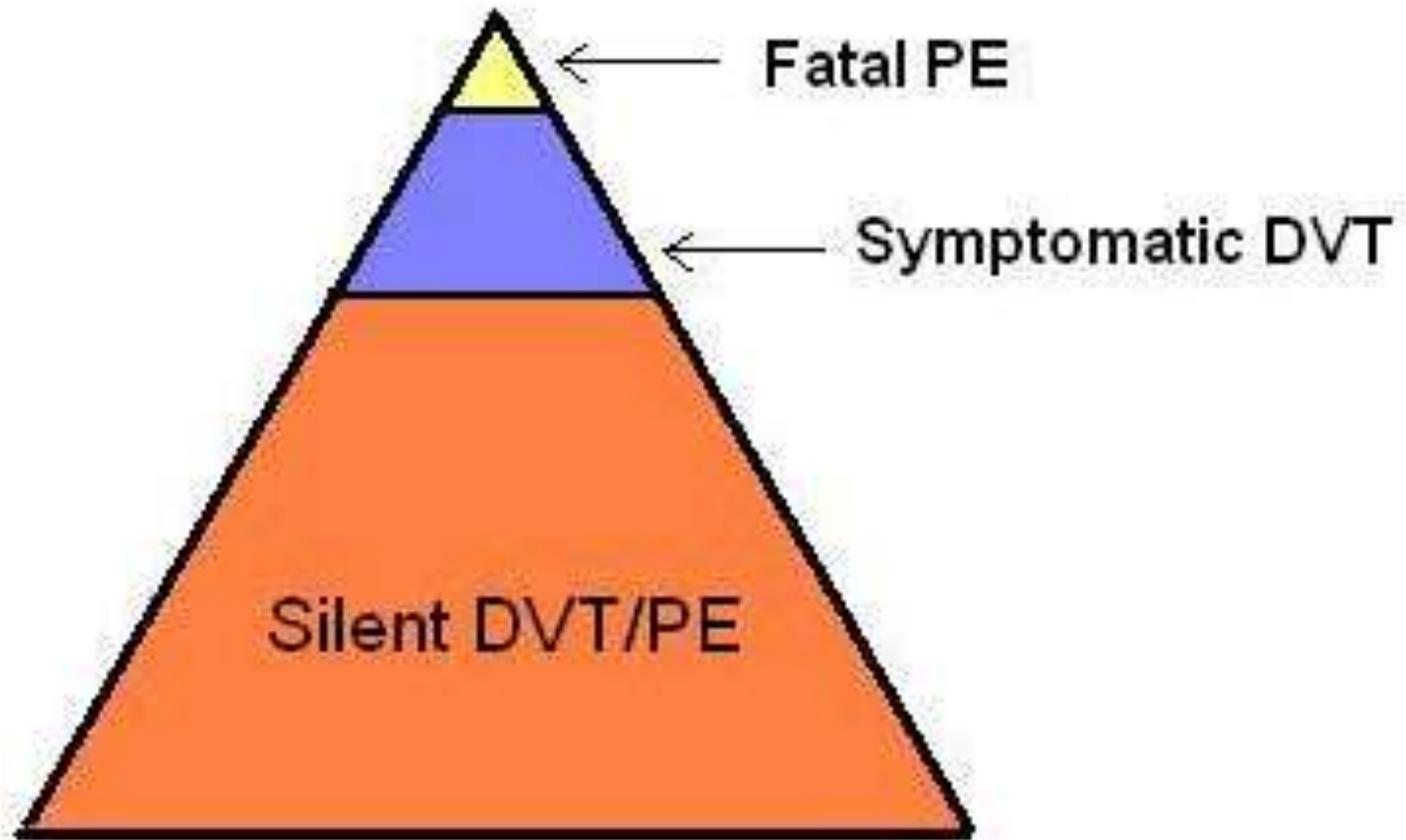
# Definition

Pulmonary embolism (PE) is a potential cardiovascular emergency caused by a sudden blockage in a lung artery by a blood clot(s) that has(ve) traveled in most cases, from the legs or, rarely, other parts of the body (deep vein thrombosis) through the bloodstream (embolism) with symptoms and signs that may include shortness of breath, rapid breathing, rapid heart rate, chest pain particularly upon breathing in, coughing up blood, low blood oxygen levels, fever, (in severe cases) abnormally low blood pressure, passing out, and sudden death, with rare long-term complications in survived patients in form of chronic thromboembolic pulmonary hypertension (CTEPH), leading to right heart failure.

# Epidemiology

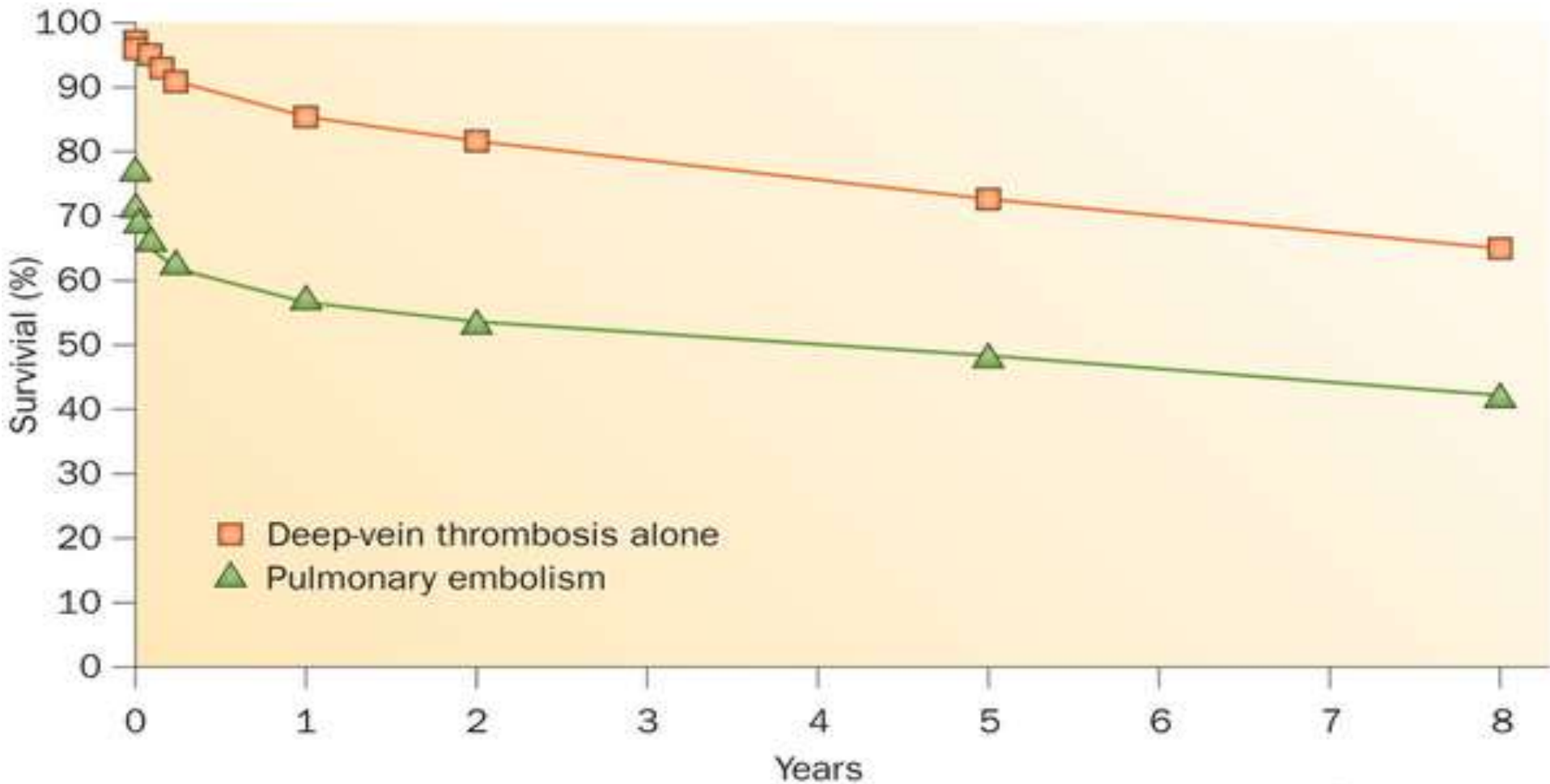
- The exact number of people affected by deep venous thrombosis (DVT) and PE isn't known
- Estimates suggest these conditions affect 300,000 to 600,000 people in the United States and 430,000 people in Europe each year
- Rates are similar in males and females and become more common as people get older
- If left untreated, about 30 percent of patients who have PE will die
- Most of those who die do so within the first few hours of the event
- A prompt diagnosis and proper treatment can save lives and help prevent the complications of PE.

# Epidemiology

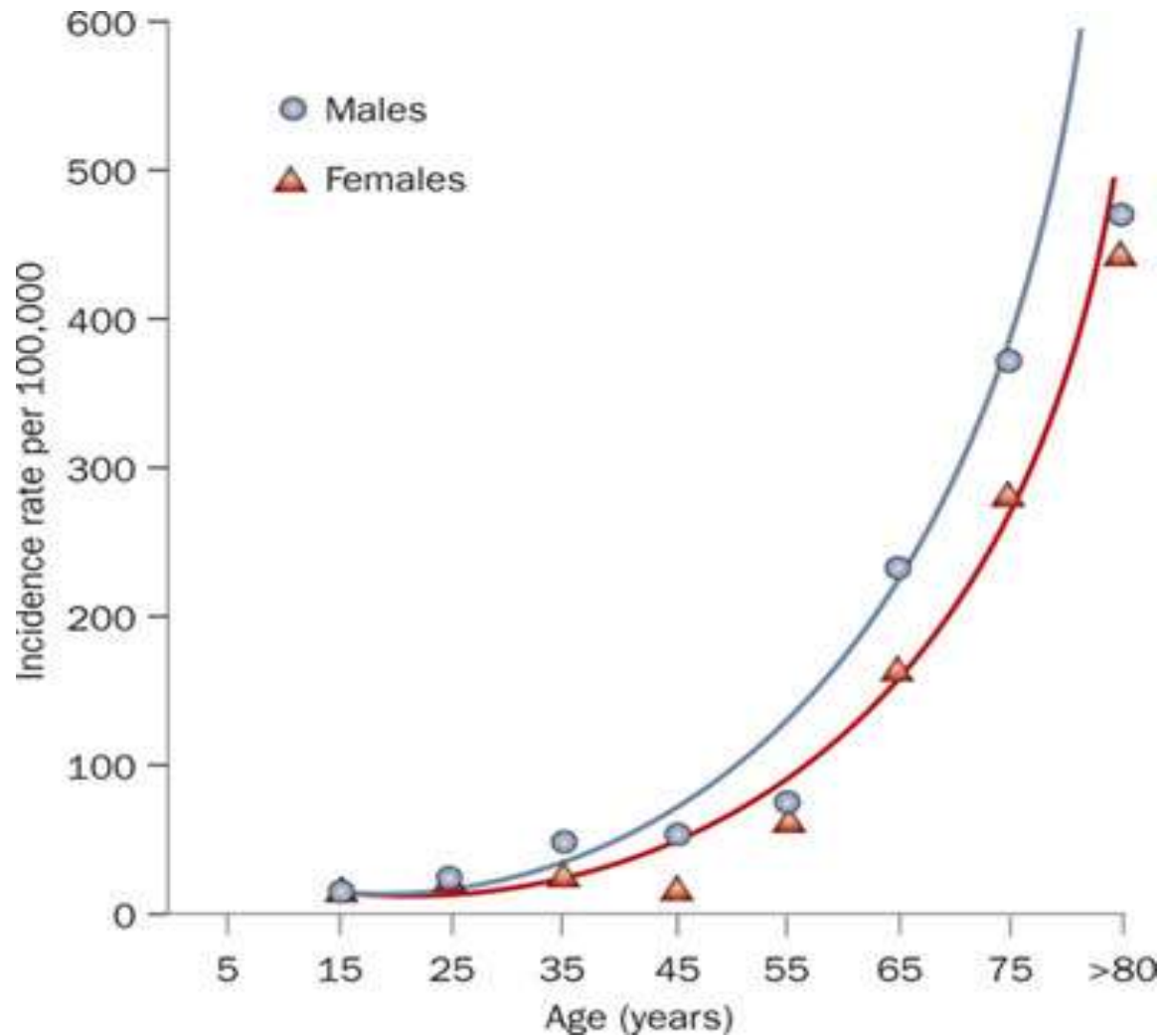


The majority of VTE events is asymptomatic; while some cases present with fatal PE.

# Epidemiology



# Epidemiology



# Risk Factors and Etiology

- Leg or pelvic vein thromboses (about 90% of emboli)
- Cancer
- A family history of embolisms
- Fractures of the leg or hip
- Hypercoagulable states or genetic blood clotting disorders, including factor V Leiden, prothrombin gene mutation, and elevated levels of homocysteine
- A history of heart attack or stroke
- Major surgery
- Obesity
- A sedentary lifestyle
- Age over 60 years
- Taking estrogen or testosterone.



# Risk Factors and Etiology

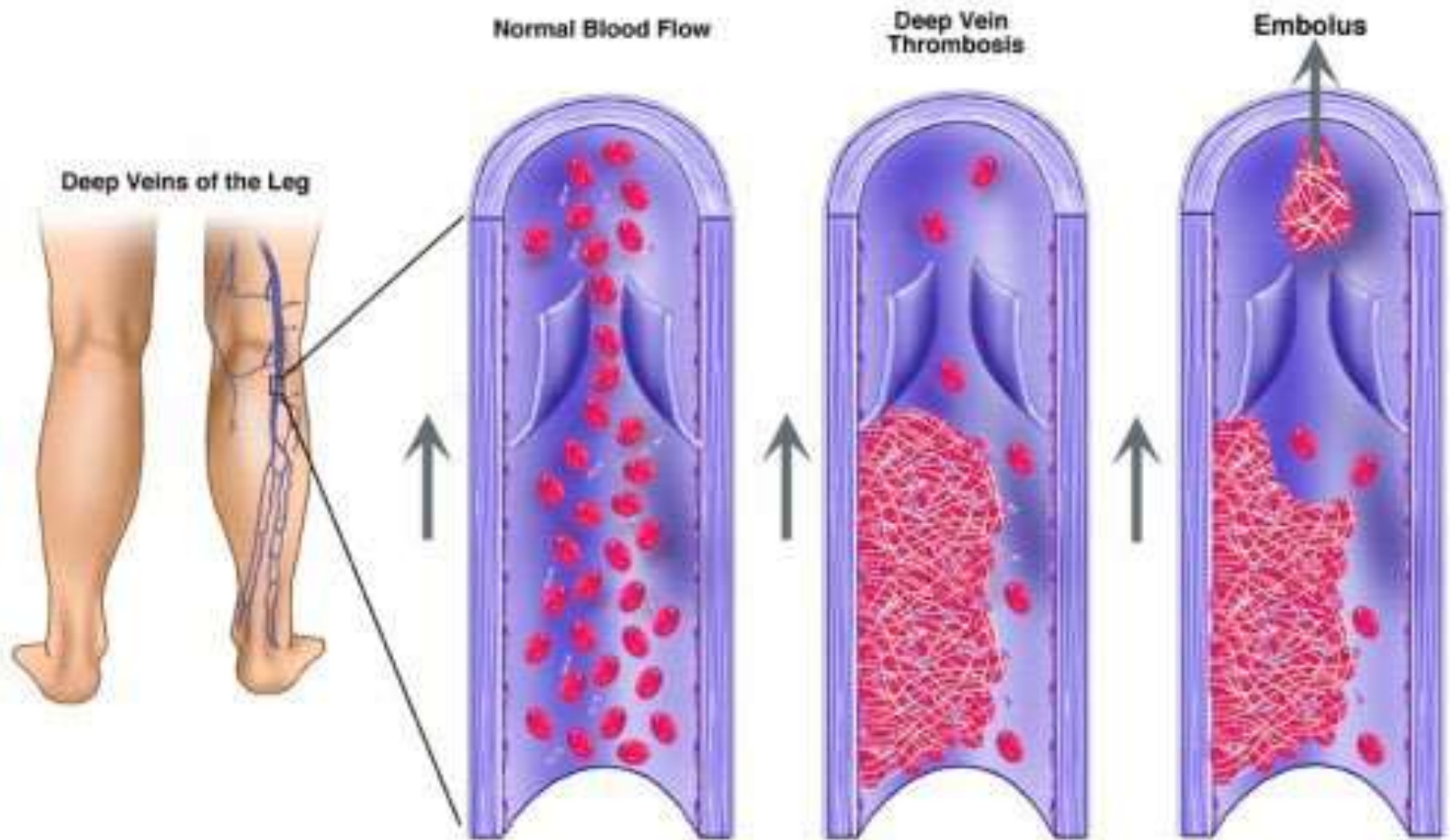
## Virchow's Triad

1. Alterations in blood flow: immobilization (after surgery), injury, pregnancy, obesity , cancer
2. Factors in the vessel wall: surgery, catheterizations
3. Factors affecting the properties of the blood: estrogen-containing hormonal contraception, genetic thrombophilia (factor V Leiden, prothrombin mutation G20210A, protein C deficiency, protein S deficiency, antithrombin deficiency, hyperhomocysteinemia and plasminogen/fibrinolysis disorders), acquired thrombophilia (antiphospholipid syndrome, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria), cancer (secretion of pro-coagulants).

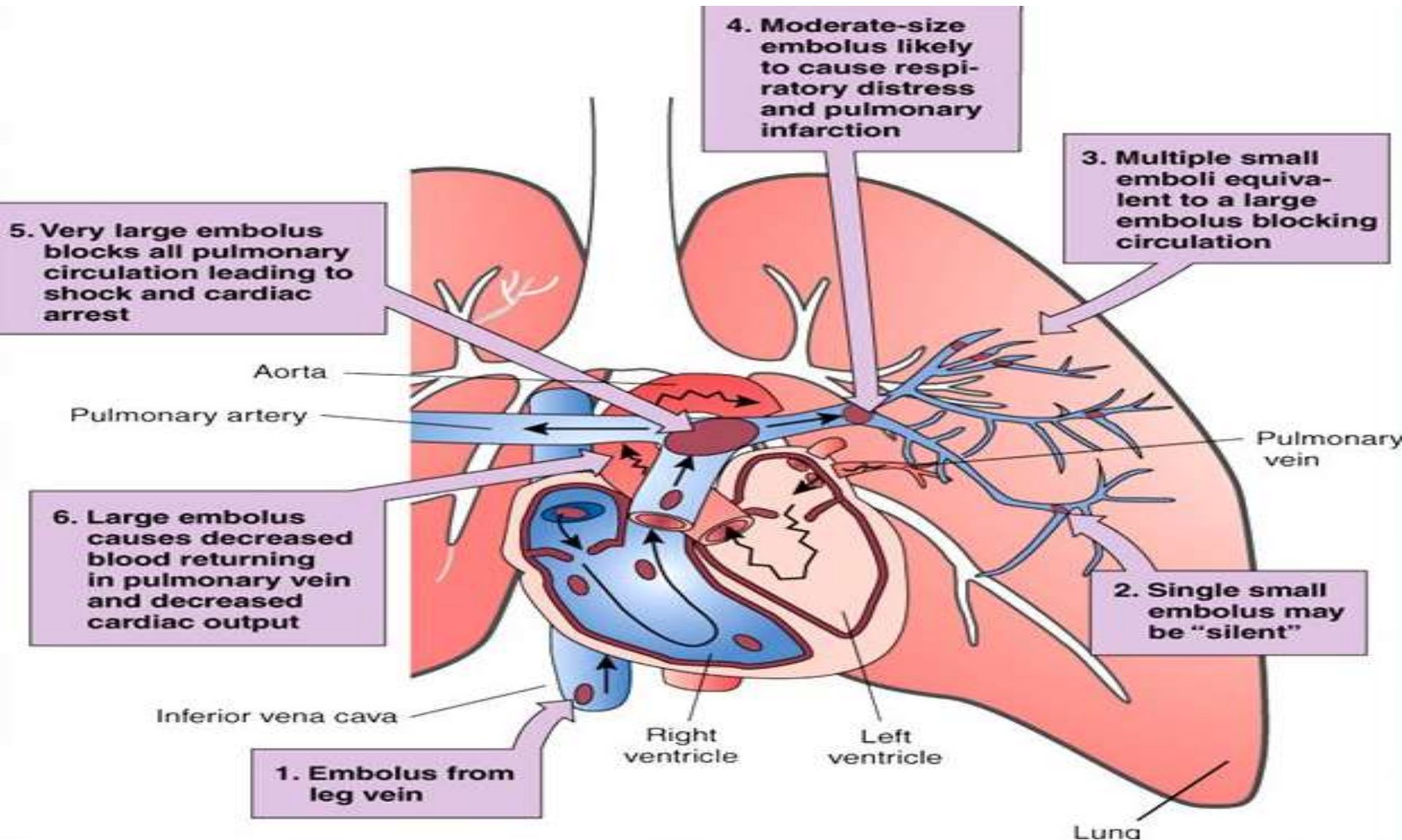
# Mechanism

- Although PE can arise from anywhere in the body, most commonly it arises from the calf veins
- The venous thrombi predominately originate in venous valve pockets (inset) and at other sites of presumed venous stasis
- Acute PE interferes with both the circulation and gas exchange
- The manifestations of PE depend upon four main factors: a) the extent of occlusion of the vascular tree, b) the patient's pre-existing cardiopulmonary condition, c) chemical vasoconstriction due to the release of serotonin and thromboxane from platelets that adhere to the embolus, as well as to fibropeptide B, which is a product of fibrinogen breakdown, d) the reflex vasoconstriction that is likely to occur as a consequence of pulmonary artery dilatation
- Right ventricular (RV) failure due to pressure overload is considered the primary cause of death in severe PE.

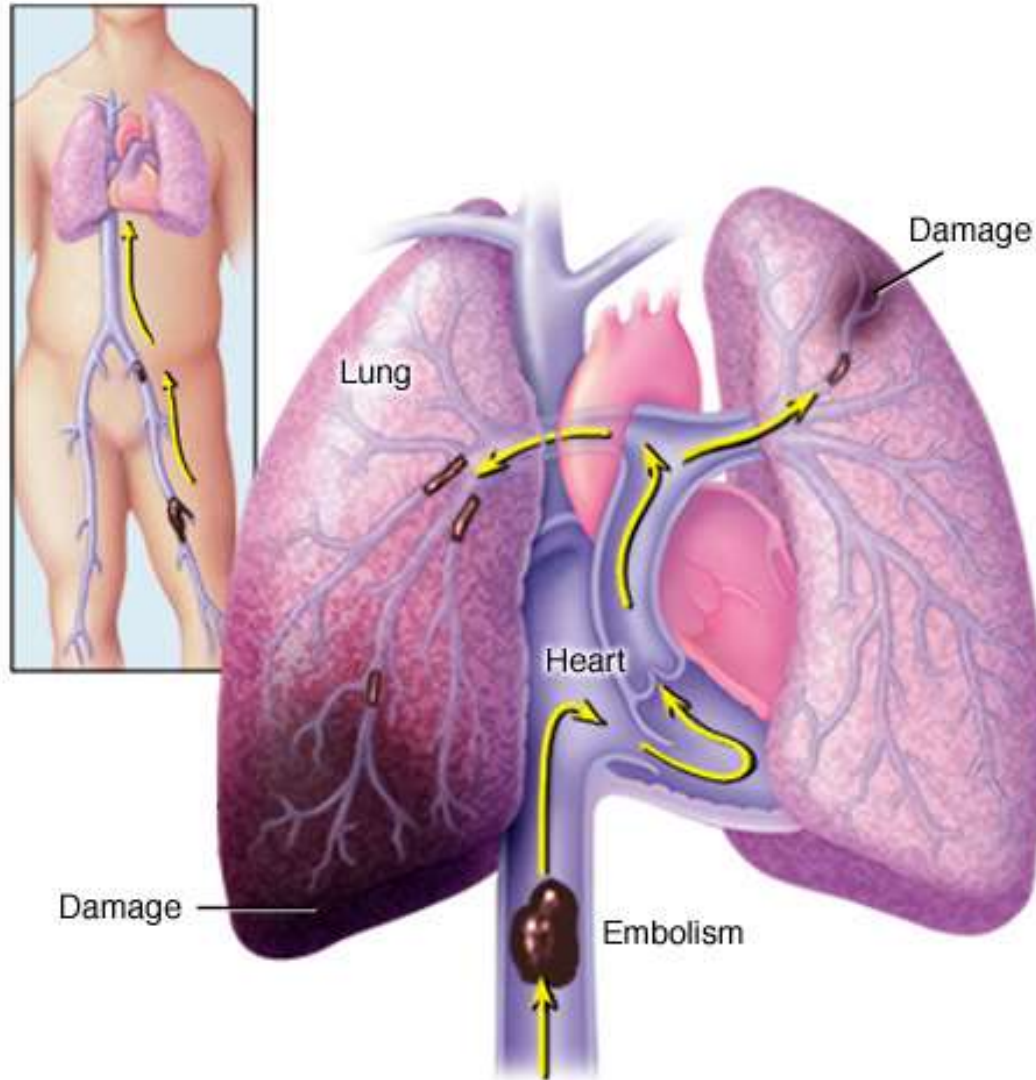
# Mechanism



# Mechanism

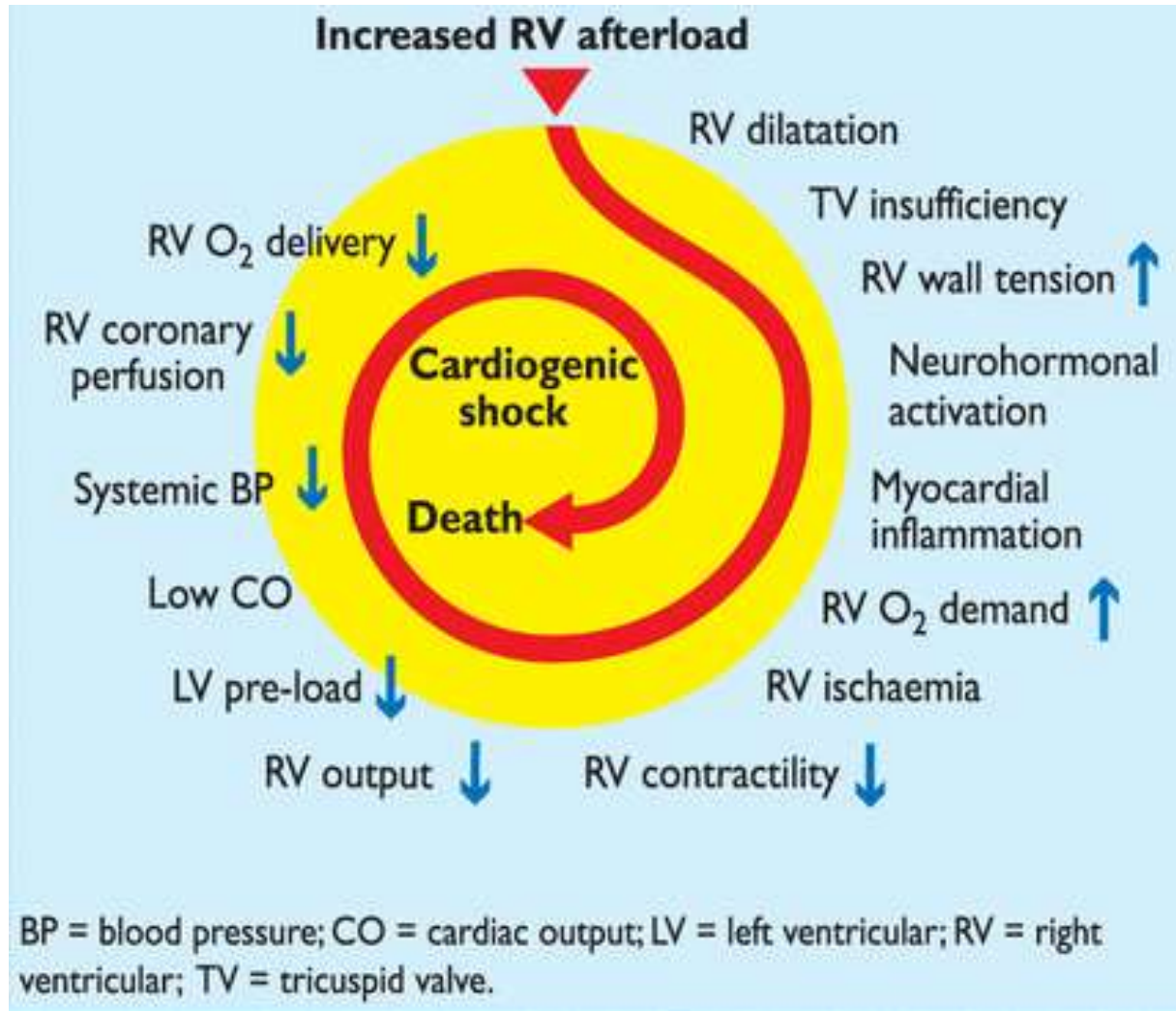


# Mechanism





# Mechanism



Key factors contributing to hemodynamic collapse in acute PE.

# Mechanism

## Respiratory Consequences

- Increased alveolar dead space
- Hypoxemia
- Hyperventilation
- Regional loss of surfactant and pulmonary infarction
- Arterial hypoxemia, that include ventilation-perfusion mismatch, intrapulmonary shunts, reduced cardiac output, and intracardiac shunt via a patent foramen ovale
- Pulmonary infarction is an uncommon consequence because of the bronchial arterial collateral circulation.

# Mechanism

## Hemodynamic Consequences

- PE reduces the cross-sectional area of the pulmonary vascular bed, resulting in an increment in pulmonary vascular resistance, which, in turn, increases the right ventricular afterload
- If the afterload is increased severely, right ventricular failure may ensue
- The humoral and reflex mechanisms contribute to the pulmonary arterial constriction
- Following the initiation of anticoagulant therapy, the resolution of emboli usually occurs rapidly during the first 2 weeks of therapy; however, it can persist on chest imaging studies for months to years
- Chronic pulmonary hypertension may occur with failure of the initial embolus to undergo lyses or in the setting of recurrent thromboemboli.



# Classification

## International Classification of Diseases

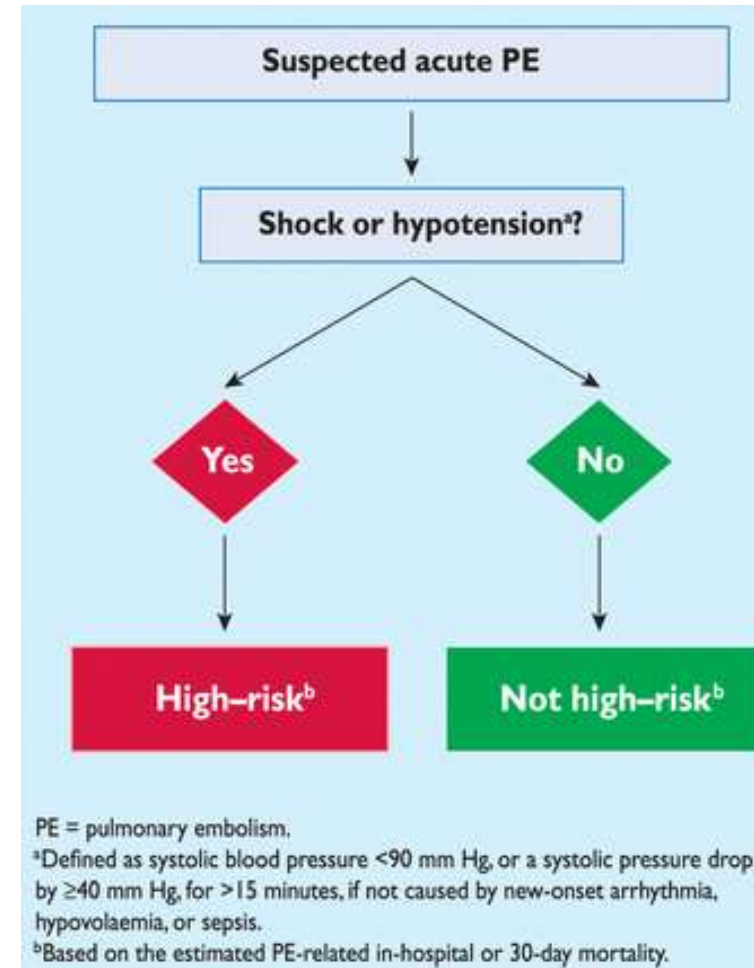
- IX Diseases of the circulatory system (I00-I99)
- Pulmonary heart disease and diseases of pulmonary circulation (I26-I28)
- 126 Pulmonary embolism
- 126.0 Pulmonary embolism with mention of acute cor pulmonale
- 126.9 Pulmonary embolism without mention of acute cor pulmonale.



# Classification

## Risk Groups

- High risk (previously 'massive') PE patients have persistent shock or hypotension
- Intermediate risk (previously 'sub-massive') PE is defined as the presence of right ventricular (RV) dysfunction and/or myocardial injury in the absence of hypotension
- Low risk PE patients have none of these features and can probably be treated outside of hospital.



# Symptoms and Signs

Symptoms of pulmonary embolism are typically sudden in onset and may include one or many of the following:

- Dyspnea (shortness of breath)
- Tachypnea (rapid breathing)
- Chest pain of a "pleuritic" nature (worsened by breathing)
- Cough
- Hemoptysis (coughing up blood)
- Cyanosis (blue discoloration, usually of the lips and fingers)
- Collapse
- Circulatory instability because of decreased blood flow through the lungs and into the left side of the heart.

# History 1

- Most DVTs start in the calf, and most probably resolve spontaneously
- Thrombi that remain confined to the calf rarely cause leg symptoms or symptomatic PE
- The probability that calf DVT will extend to involve the proximal veins and subsequently cause PE increases with the severity of the initiating prothrombotic stimulus
- Although acute VTE usually presents with either leg or pulmonary symptoms, most patients have thrombosis at both sites at the time of diagnosis
- Proximal DVTs resolve slowly during treatment with anticoagulants, and thrombi remain detectable in half of the patients after a year
- Resolution of DVT is less likely in patients with a large initial thrombus or cancer

# History 2

- 10% of patients with symptomatic DVTs develop severe post-thrombotic syndrome within 5 years
- 10% of PEs are rapidly fatal, and an additional 5% cause death later, despite diagnosis and treatment
- 50% of diagnosed PEs are associated with right ventricular dysfunction, which is associated with a  $\approx$ 5-fold greater in-hospital mortality
- There is  $\approx$ 50% resolution of PE after 1 month of treatment, and perfusion eventually returns to normal in two thirds of patients
- 5% of treated patients with PE develop pulmonary hypertension as a result of poor resolution
- After a course of treatment, the risk of recurrent thrombosis is higher in patients without reversible risk factors.

# Physical Examination 1

- The lungs are usually normal
- Occasionally, a pleural friction rub may be audible over the affected area of the lung (mostly in PE with infarct)
- A pleural effusion is sometimes present that is exudative, detectable by decreased percussion note, audible breath sounds, and vocal resonance
- Strain on the right ventricle may be detected as a left parasternal heave, a loud pulmonary component of the second heart sound, and/or raised jugular venous pressure
- A low-grade fever may be present, particularly if there is associated pulmonary hemorrhage or infarction
- The chest X-ray is frequently abnormal and, although its findings are usually non-specific in PE

# Physical Examination 2

- As smaller PE tend to lodge in more peripheral areas without collateral circulation they are more likely to cause lung infarction and small effusions (both of which are painful), but not hypoxia, dyspnea or hemodynamic instability such as tachycardia
- Larger PEs, which tend to lodge centrally, typically cause dyspnea, hypoxia, low blood pressure, fast heart rate and fainting, but are often painless because there is no lung infarction due to collateral circulation
- The classic presentation for PE with pleuritic pain, dyspnea and tachycardia is likely caused by a large fragmented embolism causing both large and small PEs
- Small PEs are often missed because they cause pleuritic pain alone without any other findings and large PEs often missed because they are painless and mimic other conditions .

# Physical Examination

## Massive Pulmonary Embolism

- Patients with massive pulmonary embolism are in shock and have systemic hypotension, poor perfusion of the extremities, tachycardia, and tachypnea
- In addition, patients appear weak, pale, sweaty, and oliguric and develop impaired mentation
- Massive pulmonary embolism has been defined by hemodynamic parameters and evidence of myocardial injury rather than anatomic findings because the former is associated with adverse outcomes
- Anatomic findings by computer tomography (CT) scan may be important in assessing risk in hemodynamically stable patients with pulmonary embolus.



# Physical Examination

## Acute Pulmonary Infarction

- Approximately 10% of patients have peripheral occlusion of a pulmonary artery, causing parenchymal infarction
- These patients present with acute onset of pleuritic chest pain, breathlessness, and hemoptysis
- Although the chest pain may be clinically indistinguishable from ischemic myocardial pain, normal electrocardiography findings and no response to nitroglycerin rules out myocardial pain
- Patients with acute pulmonary infarction have decreased excursion of the involved hemithorax, palpable or audible pleural friction rub, and even localized tenderness
- Signs of pleural effusion, such as dullness to percussion and diminished breath sounds, may be present.

# Physical Examination

## Acute Embolism without Infarction

- Patients with acute embolism without infarction have nonspecific physical signs that may easily be secondary to another disease process
- Tachypnea and tachycardia frequently are detected, pleuritic pain sometimes may be present, crackles may be heard in the area of embolization, and local wheeze may be heard rarely.

# Physical Examination

## Multiple Pulmonary Emboli or Thrombi

- Patients with pulmonary emboli and thrombi have physical signs of pulmonary hypertension and cor pulmonale
- Patients may have elevated jugular venous pressure, right ventricular heave, palpable impulse in the left second intercostal space, right ventricular S<sub>3</sub> gallop, systolic murmur over the left sternal border that is louder during inspiration, hepatomegaly, ascites, and dependent pitting edema
- These findings are not specific for pulmonary embolism and require a high index of suspicion for pursuing appropriate diagnostic studies.

# Complications

- Cardiac arrest and sudden death
- Shock
- Abnormal heart rhythms
- Pulmonary infarction
- Pleural effusion
- Paradoxical embolism
- Pulmonary hypertension.

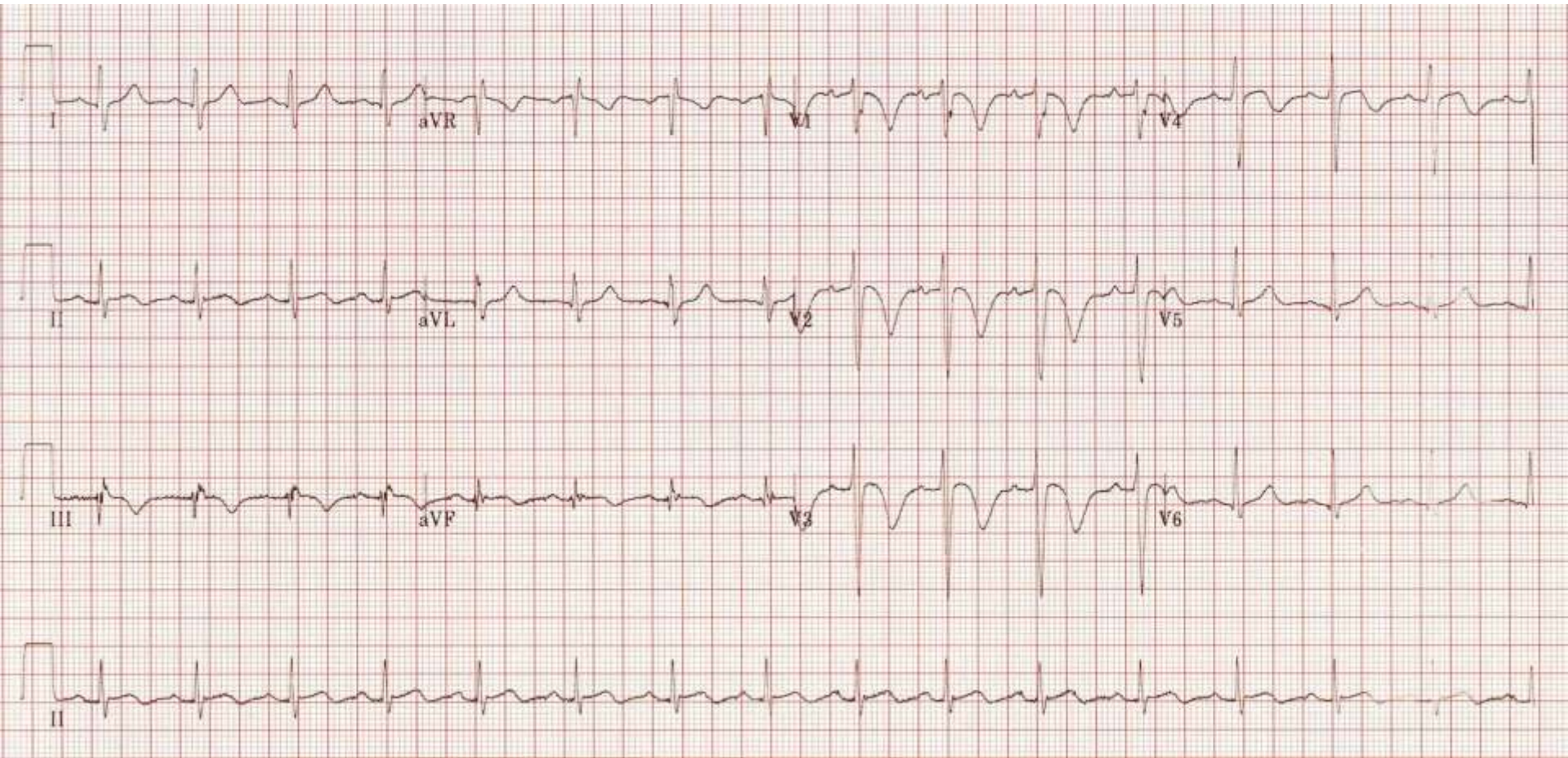
# Diagnosis

## Clinical Presentation

- PE may escape prompt diagnosis since the clinical signs and symptoms are non-specific
- When the clinical presentation raises the suspicion of PE in an individual patient, it should prompt further objective testing
- In most patients, PE is suspected on the basis of dyspnea, chest pain, pre-syncope or syncope, and/or hemoptysis
- Knowledge of the predisposing factors for VTE is important in determining the likelihood of PE
- In blood gas analysis, hypoxemia is considered a typical finding in acute PE, but up to 40% of the patients have normal arterial oxygen saturation and 20% a normal alveolar-arterial oxygen gradient
- Electrocardiographic changes indicative of RV strain, and incomplete or complete right bundle-branch block, may be helpful ; atrial arrhythmias, may be associated with acute PE.

# Diagnosis

## Electrocardiographic Changes



Sinus tachycardia, simultaneous T-wave inversions in the anterior (V1-4) and inferior leads (II, III, aVF), non-specific ST changes – slight ST elevation in III and aVF.

# Diagnosis

## Assessment Of Clinical Probability

- Despite the limited sensitivity and specificity of individual symptoms, signs, and common tests, the combination of findings evaluated by clinical judgement or by the use of prediction rules allows to classify patients with suspected PE into distinct categories of clinical or pre-test probability that correspond to an increasing actual prevalence of confirmed PE
- As the post-test (e.g. after computed tomography) probability of PE depends not only on the characteristics of the diagnostic test itself but also on pre-test probability, this has become a key step in all diagnostic algorithms for PE.

# Diagnosis

## Clinical Probability Scoring: The Wells' Score

Variable	Points
Clinical signs and symptoms of DVT*	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate >100 beats per minute	1.5
Immobilization or surgery in previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (on treatment, treated in the last 6 mos or palliative)	1.0

*\*Minimum of leg swelling and pain with palpation of deep veins; DVT, deep-vein thrombosis; PE, pulmonary embolism*

Score	Category	Score	Category
<2 points	low probability	<4 points	unlikely PE
2–6 points	moderate probability	≥4 points	likely PE
>6 points	high probability		



# Diagnosis

## D-dimer Testing

- D-dimer levels are elevated in plasma in the presence of acute thrombosis because of simultaneous activation of coagulation and fibrinolysis
- The negative predictive value of D-dimer testing is high and a normal D-dimer level renders acute PE or DVT unlikely
- On the other hand, fibrin is also produced in a wide variety of conditions such as cancer, inflammation, bleeding, trauma, surgery and necrosis
- Accordingly, the positive predictive value of elevated D-dimer levels is low and D-dimer testing is not useful for confirmation of PE.

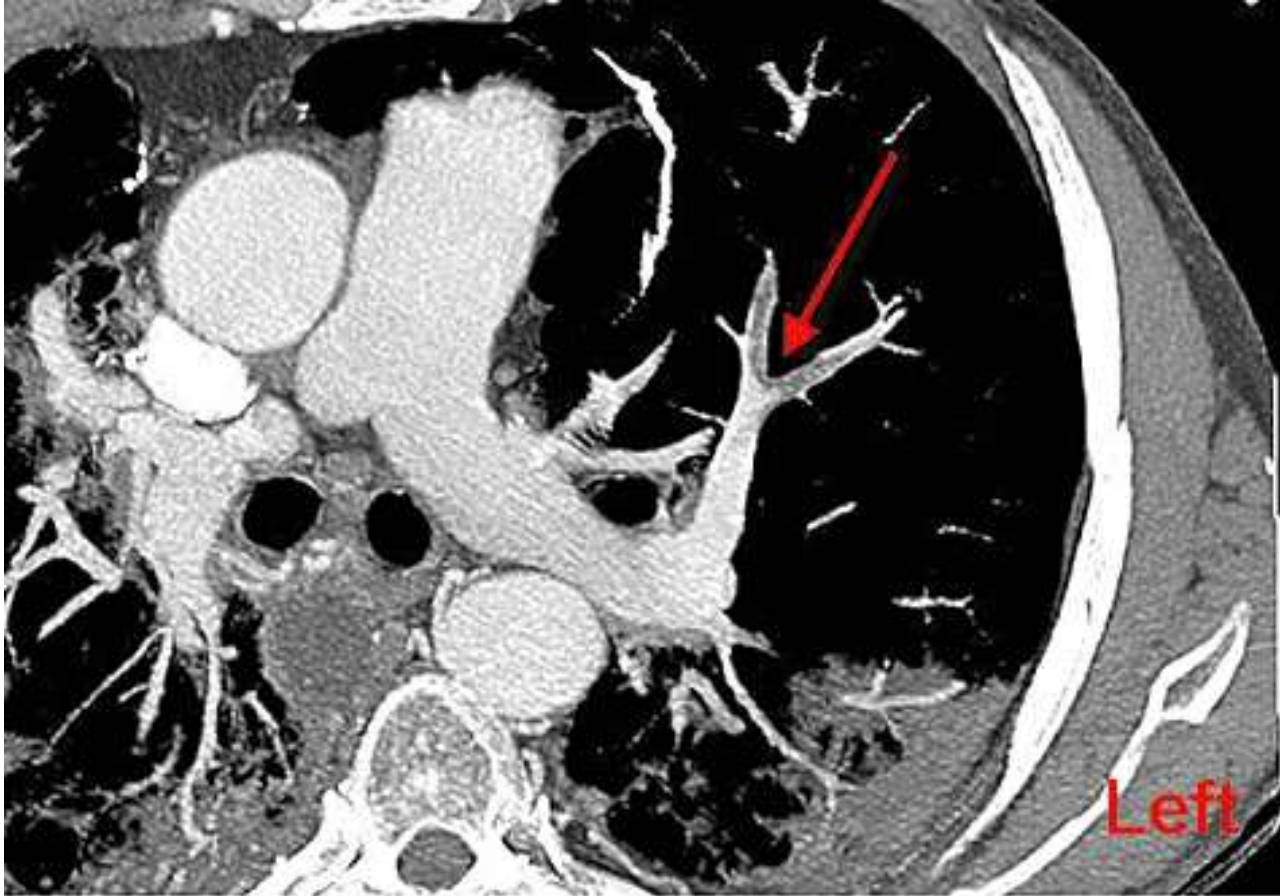
# Diagnosis

## Computed Tomographic Pulmonary Angiography

- Since the introduction of multi-detector computed tomographic (MDCT) angiography with high spatial and temporal resolution and quality of arterial opacification, CT angiography has become the method of choice for imaging the pulmonary vasculature in patients with suspected PE
- It allows adequate visualization of the pulmonary arteries down to at least the segmental level.

# Diagnosis

## Multi-detector Computed Tomographic Angiography



Pulmonary emboli in the middle and in the anterior branches of the left lung (arrow), and several lung nodules in both lungs.

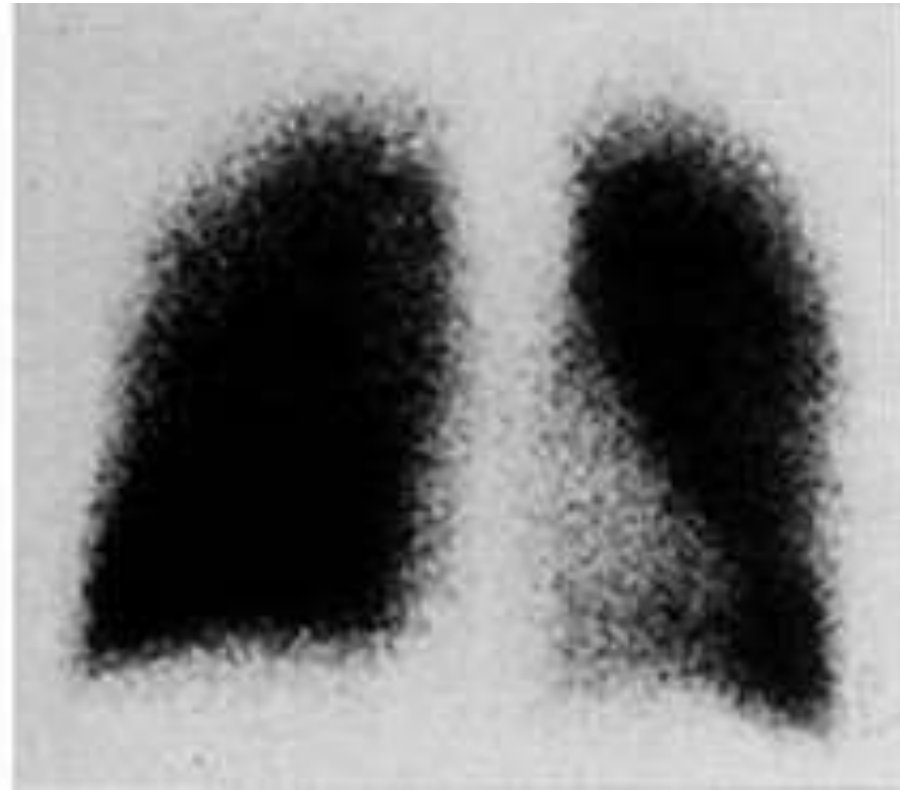
# Diagnosis

## Lung Scintigraphy

- Ventilation–perfusion scintigraphy (V/Q scan) is an established diagnostic test for suspected PE
- V/Q scan is safe and few allergic reactions have been described
- The test is based on the intravenous injection of technetium (Tc)-99m-labelled macroaggregated albumin particles, which block a small fraction of the pulmonary capillaries and thereby enable scintigraphic assessment of lung perfusion
- Perfusion scans are combined with ventilation studies, for which multiple tracers such as xenon-133 gas, Tc-99m-labelled aerosols, or Tc-99m-labelled carbon microparticles (Technegas) can be used

# Diagnosis

## Ventilation–perfusion Scintigraphy



An abnormal nuclear lung scan shows areas without nuclear particles (arrows). This finding indicates that pulmonary emboli (blood clots) may be present. A normal lung scan is shown on the right for comparison.

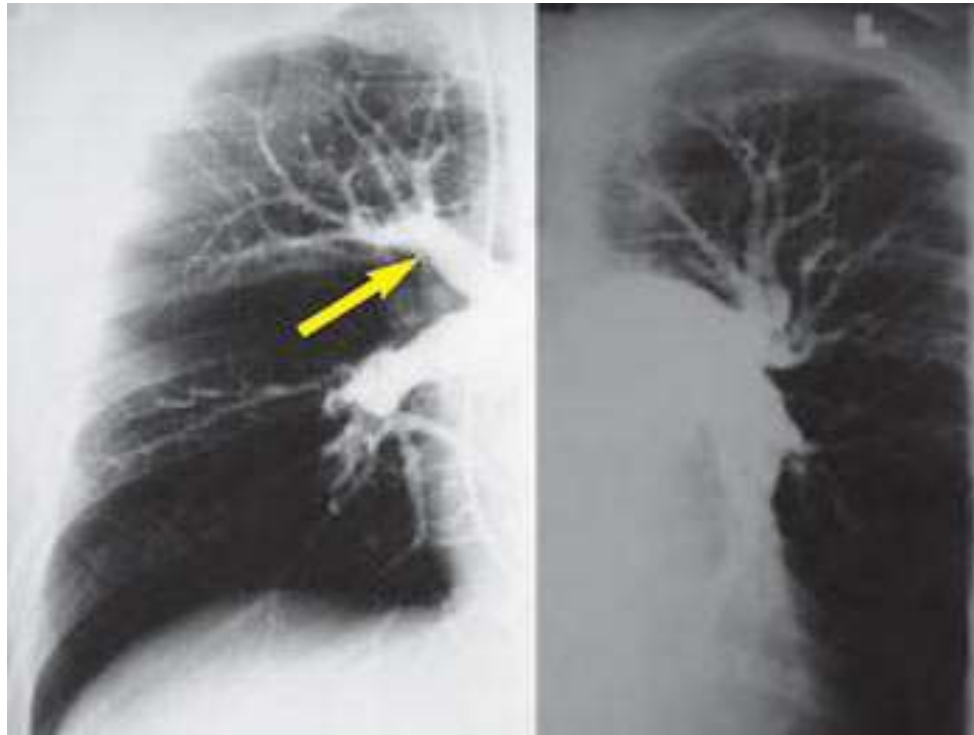
# Diagnosis

## Pulmonary Angiography

- Pulmonary angiography has for decades remained the 'gold standard' for the diagnosis or exclusion of PE, but is rarely performed now as less-invasive CT angiography offers similar diagnostic accuracy
- The diagnosis of acute PE is based on direct evidence of a thrombus in two projections, either as a filling defect or as amputation of a pulmonary arterial branch
- Thrombi as small as 1–2 mm within the sub-segmental arteries can be visualized , but there is substantial inter-observer variability at this level
- Indirect signs of PE, such as slow flow of contrast, regional hypoperfusion, and delayed or diminished pulmonary venous flow, are not validated and hence are not diagnostic.

# Diagnosis

Pulmonary angiography as the 'gold standard' for the diagnosis or exclusion of PE



Organized thrombi appear as unusual filling defects, webs, or bands, or completely thrombosed vessels that may resemble congenital absence of the vessel.

# Diagnosis

## Magnetic Resonance Angiography

- Magnetic resonance angiography (MRA) has been evaluated for several years in suspected PE but large-scale studies were published only recently
- Their results show that this technique, although promising, is not yet ready for clinical practice due to its low sensitivity, high proportion of inconclusive MRA scans, and low availability in most emergency settings .



# Diagnosis

## Ventilation–perfusion Scintigraphy

An abnormal nuclear lung scan shows areas without nuclear particles (arrows). This finding indicates that pulmonary emboli (blood clots) may be present. A normal lung scan is shown on the right for comparison.

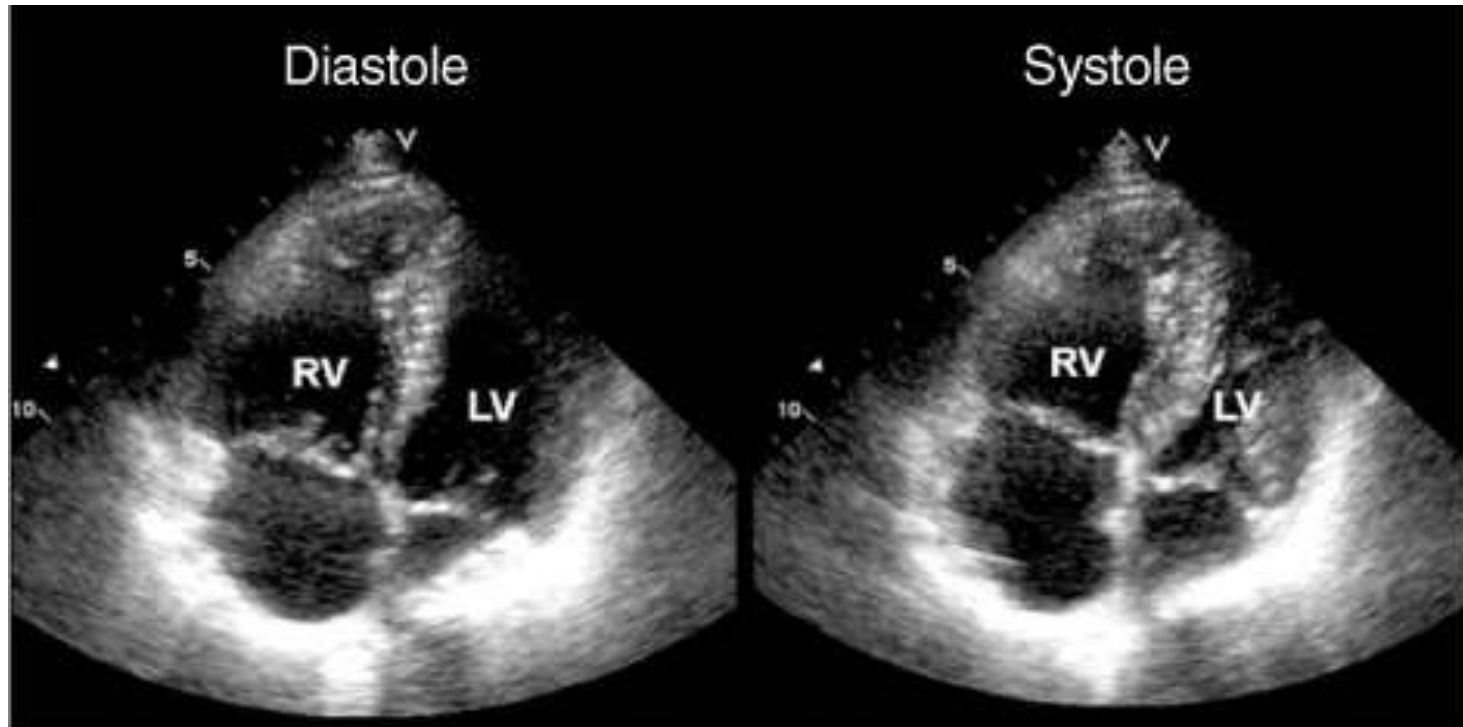
# Diagnosis

## Echocardiography

- Acute PE may lead to right ventricle (RV) pressure overload and dysfunction, which can be detected by echocardiography
- Given the peculiar geometry of the RV, there is no individual echocardiographic parameter that provides fast and reliable information on RV size or function
- Signs of RV overload or dysfunction may also be found in the absence of acute PE and be due to concomitant cardiac or respiratory disease.

# Diagnosis

## Echocardiography Signs



A patient with acute pulmonary thromboembolism. In the diastole, the ratio of the right ventricular end-diastolic area to left ventricular end-diastolic area was more than 1.0 which is consistent with severe right ventricular dysfunction (normal value is less than 0.6).

# Diagnosis

## Validated Diagnostic Criteria

Diagnostic criterion	Clinical probability of PE				
	Low	Intermediate	High	PE unlikely	PE likely
<b>Exclusion of PE</b>					
<b>D-dimer</b>					
Negative result, highly sensitive assay	+	+	–	+	–
Negative result, moderately sensitive assay	+	±	–	+	–
<b>Chest CT angiography</b>					
Normal multidetector CT alone	+	+	±	+	±
<b>V/Q scan</b>					
Normal perfusion lung scan	+	+	+	+	+
Non-diagnostic lung scan <sup>a</sup> and negative proximal CUS	+	±	–	+	–
<b>Confirmation of PE</b>					
Chest CT angiogram showing at least segmental PE	+	+	+	+	+
High probability V/Q scan	+	+	+	+	+
CUS showing proximal DVT	+	+	+	+	+

# Diagnosis

## Differentiation

- Acute Coronary Syndrome
- Acute Pericarditis
- Acute Respiratory Distress Syndrome
- Angina Pectoris
- Anxiety Disorders
- Aortic Stenosis
- Atrial Fibrillation
- Cardiogenic Shock
- Cor Pulmonale
- Dilated Cardiomyopathy
- Emphysema
- Fat Embolism
- Hypersensitivity Pneumonitis
- Mitral Stenosis
- Myocardial Infarction
- Pneumothorax Imaging
- Pulmonary Arterial Hypertension
- Pulmonary Arteriovenous Fistulae
- Restrictive Cardiomyopathy
- Sudden Cardiac Death
- Superior Vena Cava Syndrome in Emergency Medicine
- Syncope

# Management

- Anticoagulant therapy is the mainstay of treatment
- Acutely, supportive treatments, such as oxygen or analgesia, may be required
- People are often admitted to hospital in the early stages of treatment, and tend to remain under inpatient care until the international normalized ratio (INR) has reached therapeutic levels
- Increasingly, however, low-risk cases are managed at home in a fashion already common in the treatment of DVT
- Evidence to support one approach versus the other is weak.

# Management

## Anticoagulation

- Anticoagulant therapy is the mainstay of treatment (heparin, low molecular weight heparin (LMWH), fondaparinux, warfarin, acenocoumarol, or phenprocoumon)
- LMWH may reduce bleeding among people with pulmonary embolism as compared to heparin
- Warfarin therapy often requires a frequent dose adjustment and monitoring of the INR: INRs between 2.0 and 3.0 are generally considered ideal
- In patients with an underlying malignancy, therapy with a course of LMWH is favored over warfarin
- Similarly, pregnant women are often maintained on low molecular weight heparin until at least six weeks after delivery to avoid the known teratogenic effects of warfarin, especially in the early stages of pregnancy.

# Management

## Thrombolysis

- Massive PE causing hemodynamic instability is an indication for thrombolysis, the enzymatic destruction of the clot with medication
- Catheter-directed thrombolysis (CDT) is a new technique found to be relatively safe and effective for massive PEs
- Medication that breaks up blood clots is released through the catheter so that its highest concentration is directly next to the pulmonary embolus
- CDT is performed by interventional radiologists, and in medical centers that offer CDT, it should be considered first-line treatment
- The use of thrombolysis in non-massive PEs is still debated.



# Management

## Inferior Vena Cava Filter

- There are two situations when an inferior vena cava filter is considered advantageous, and those are if anticoagulant therapy is contraindicated (e.g. shortly after a major operation), or a person has a pulmonary embolus in spite of being anticoagulated.
- In these instances, it may be implanted to prevent new or existing DVTs from entering the pulmonary artery and combining with an existing blockage
- Inferior vena cava filters should be removed as soon as it becomes safe to start using anticoagulation.
- Although modern filters are meant to be retrievable, complications may prevent some from being removed
- The long-term safety profile of permanently leaving a filter inside the body is not known.

# Management

## Surgery

- Surgical management of acute PE (pulmonary thrombectomy) is uncommon and has largely been abandoned because of poor long-term outcomes
- However, recently, it has gone through a resurgence with the revision of the surgical technique and is thought to benefit certain people
- Chronic PE leading to pulmonary hypertension (known as *chronic thromboembolic hypertension*) is treated with a surgical procedure known as a pulmonary thromboendarterectomy.

# Prognosis

- Less than 5 to 10% of symptomatic PEs are fatal within the first hour of symptoms
- Prognosis depends on the amount of lung that is affected and on the co-existence of other medical conditions; chronic embolization to the lung can lead to pulmonary hypertension
- Once anticoagulation is stopped, the risk of a fatal pulmonary embolism is 0.5% per year
- Mortality from untreated PEs was said to be 26%.

# Prophylaxis

- PE may be preventable in those with risk factors
- People admitted to hospital may receive preventative medication, including unfractionated heparin, low molecular weight heparin, or fondaparinux, and anti-thrombosis stockings to reduce the risk of a DVT in the leg that could dislodge and migrate to the lungs
- Following the completion of warfarin in those with prior PE, long-term aspirin is useful to prevent recurrence.

# Abbreviations

DVT - deep venous thrombosis

CDT - catheter-directed thrombolysis

CT - computed tomography

CTEPH - chronic thromboembolic pulmonary hypertension

INR - international normalized ratio

LMWH - low molecular weight heparin

MDCT - multi-detector computed tomography

MRA - magnetic resonance angiography

PE - pulmonary embolism

RV - right ventricle

VTE - venous thromboembolism

V/Q scan - ventilation–perfusion scintigraphy

# Diagnostic and treatment guidelines

[Acute pulmonary embolism](#)

[2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism](#)

[Pulmonary Embolism Guidelines](#)

[Pulmonary Embolism Treatment & Management](#)

[Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension](#)

[Evaluation of Patients With Suspected Acute Pulmonary Embolism: Best Practice Advice From the Clinical Guidelines Committee of the American College of Physicians](#)